

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
7 August 2003 (07.08.2003)

PCT

(10) International Publication Number
WO 03/063851 A1

- (51) International Patent Classification⁷: **A61K 31/13**, A23L 1/03, A61K 7/06 (74) Agents: **APPOLONI, Ramono** et al.: Marchi & Partners, S.r.l., Via Pirelli, 19, I-20124 Milano (IT).
- (21) International Application Number: PCT/EP03/00519 (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (22) International Filing Date: 17 January 2003 (17.01.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: M120002A000189 1 February 2002 (01.02.2002) IT (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
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- Published:**
— with international search report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: COMPOSITION FOR PHARMACEUTICAL OR DIETETIC USE FOR COMBATING HAIR LOSS

(57) Abstract: The present invention relates to a novel use of the polyamine known as spermidine, i.e. N-(3-aminopropyl)tetraethylenediamine, as an active principle in the preparation of a composition for pharmaceutical or dietetic use in man for combating hair loss.

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"Composition for pharmaceutical or dietetic use for combating hair loss"

* * * * *

The present invention relates to a novel use of the polyamine known as spermidine, i.e. N-(3-aminopropyl)tetramethylenediamine.

It is known in the literature that compounds belonging to the class of aliphatic polyamines play a deciding role in controlling the biological mechanisms of growth, division and differentiation of cells and proliferation of animal tissues.

The polyamines in question essentially comprise the compounds putrescine, spermine and spermidine. The latter compound, i.e. N-(3-aminopropyl)tetramethylenediamine, owes its name to the fact that it was first discovered in human sperm. In reality, it is present in virtually all the bodily fluids (blood, saliva, tears and milk). It was subsequently also found in many foods of both animal origin (meat, fish, eggs, milk and cheese) and plant origin (fruit and vegetables). It is of particularly high concentration in human milk (on average about 600 micrograms in milk over 24 hours), where it plays an important role for the newborn. Specifically, in the newborn, the mucosae of the digestive tract are not fully formed and spermidine, taken up with the milk, promotes the growth of the epithelium of the gastric and intestinal mucosa.

Spermidine is therefore an important factor in the growth and proliferation of cells.

According to the present invention, it has now been found, surprisingly, that a preparation containing spermidine, administered orally to man, results in a stimulation of the hair bulbs with consequent promotion of hair growth, in particular in the case of a pathological hair loss such as that known as telogenic defluvium, characterized by a state of suffering of the hair bulb, leading to an abnormal and excessive loss of hair.

One subject of the present invention is, thus, the use of

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spermidine as an active principle in the preparation of a composition for pharmaceutical or dietetic use in man to combat pathological hair loss, in particular in the case of telogenic defluvium.

5 A subject of the present invention is also a composition for pharmaceutical or dietetic use to be administered to man to combat pathological hair loss, characterized in that it comprises spermidine as active principle.

To understand the characteristics and advantages of the invention more clearly, an experimental study from which they are derived will
10 now be described in greater detail.

To this end, a few fundamental notions regarding the phases of growth of a hair should first be presented. The growth cycle of hair consists essentially of three phases, during which the hair follicle passes from periods of intense growth to periods of quiescence and
15 then of involution. These three phases are: the anagenic phase, i.e. the phase of hair growth, during which there are a number of changes in the dermal papilla in which the cells undergo intense metabolic activity. The hairs grow 0.3-0.4 mm per day. The hairs are not all in the same growth phase, but rather they alternate. The anagenic phase lasts from
20 3 to 6 years.

The catagenic phase is the phase of involution lasting from 2 to 3 weeks, during which the hair follicle undergoes profound morphological and metabolic changes. The lower segment is lost, the length of the follicle is reduced by about a third, the bulb decreases in size, the
25 melanocytes stop producing pigment and the papilla becomes atrophic: the hair falls out.

Finally, the telogenic phase is the resting phase, during which the hair follicle is completely inactive. The hair is inside the hair follicle, held by weak intercellular bonds that cause it to stay in the scalp until the
30 start of the new anagenic phase and sometimes even for several

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successive phases. The telogenic phase lasts from 2 to 4 months.

Every day about 50 hairs die and fall out, and, under normal conditions, are immediately replaced by new members, since the follicles have mutually synchronized life cycles such that the total
5 volume of hairs remains virtually unchanged. In this way, total exchange of the hairs takes place every 2-6 months.

The concept of telogenic defluvium was first introduced by Kligman in 1961. Before that time, it was difficult to distinguish the causes of excessive hair loss (owing to metabolic disturbances,
10 intoxication or infection) from the other more general forms of alopecia.

The diagnosis of telogenic defluvium is made by taking into consideration the growth phases of the hair. When, for various reasons, the anagenic and telogenic phases are altered (and this may take place in both senses: either they are excessively faster or excessively slower
15 than the norm), this results in the phenomenon of telogenic defluvium, which is distinguished by excessive hair loss and by profound morphological alterations in the hair.

The factors that can lead to an imbalance in the hair cycles, with consequent onset of telogenic defluvium, may be: particular
20 physiological conditions (pregnancy), prolonged states of stress and anxiety, use of certain drugs such as, for example, bromocryptine, cimetidine, levodopa, etretinate, lithium, pyridostigmine, propranolol and anti-thyroid drugs, non-balanced diets and deficiencies in vitamins and minerals.

25 The morphological alterations in the hair during telogenic defluvium may be a microscopically visible destructuring of the shaft, with a consequent reduced mechanical tensile strength and reduced elasticity; alterations in the trichogram; mineral deficiencies, or histological alterations in the hair bulb.

30

CLINICAL STUDY

This controlled, randomized double-blind study was performed according to the present invention by means of the protocols below.

Sixty volunteers of both sexes and ranging between 18 and 60
5 years old were divided into three groups of 20 individuals each, all having the same level of pathology, i.e. telogenic defluvium existing for at least 2 months.

Some of these individuals were treated for 60 days with one capsule a day of a composition of the invention, according to the
10 following scheme:

Group 1: 20 individuals treated with a composition of the invention containing spermidine alone (0.50 mg per capsule).

Group 2: 20 individuals treated with a composition of the invention according to Example 1 described later (spermidine 0.50 mg per
15 capsule).

Group 3: 20 individuals treated with a placebo, in capsules.

The parameters evaluated were the following:

- A) General dermatological visit.
- B) Microscopic evaluation of the shaft of the hairs (diameter and
20 possible structural changes in the hair).
- C) Trichogram, i.e. evaluation of the bulbs in the anagenic (growth) phase, catagenic (involutional stasis) phase, telogenic (pathological precocious hair loss) phase and exogenic (physiological loss of hairs since they are replaced with new hairs).
- 25 D) Haematochemical analysis.
- E) Pull test (mechanical tensile strength of the hair).
- F) Wash test (count of the hairs lost after washing with shampoo).
- G) Possible side effects.

These parameters were evaluated at time T_0 (before the start of
30 the treatment); at time T_1 (at the end of the 60 days of treatment); and

finally at time T_2 (30 days after stopping the administration).

The results were as follows:

- 5 A) The dermatological visit revealed an appreciable and significant reduction in the hair loss and an improvement in the structure of the shaft in the groups of patients 1 and 2 compared with the placebo group 3.
- 10 B) Microscopic evaluation of the shaft
The diameter of the hair shaft increases quite substantially in groups 1 and 2, whereas it remains virtually unchanged in the placebo group 3.
- 15 C) The trichogram is the parameter that, together with the wash test, gave the most interesting results. In this regard, reference is made to the diagrams of Figures 1 and 2 in the attached drawings. These show the trichogram of the anagenic and telogenic phases at times T_0 (before the start of the treatment); at time T_1 (at the end of the 60 days of treatment); and finally at time T_2 (30 days after stopping the administration) for the individuals of the three groups, 1 (grey column), 2 (black column) and 3 (pale column). The percentage of hairs in the anagenic phase (Fig. 1) and in the telogenic phase (Fig. 2) for the treated individuals belonging to the three groups under consideration is shown on the y-axis, and the said times T are shown on the x-axis, under which are tabulated the said percentages found.
- 20 Specifically, the microscopic analysis of the state of the bulb reveals that the number of bulbs in the anagenic phase increases significantly in Groups 1 and 2 and, in parallel, in the same Groups, the telogenic phase decreases significantly. In contrast, in the placebo group 3, the anagenic and telogenic phases are not significantly changed.
- 30 In particular, a 17.2% increase in the anagenic phase at T_2 relative

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to T_0 (with an 8.1% increase at T_1) was found in Group 1.

A 20.2% increase in the anagenic phase at T_2 relative to T_0 (with an 8.12% increase at T_1) was found in Group 2.

5 A 7.79% increase in the anagenic phase at T_2 relative to T_0 (with a 2.7% increase at T_1) was found in Group 3. The change of about 7.79% in the anagenic phase from T_0 to T_2 in the placebo group is comparable to the cyclic changes that take place within the hair bulbs.

In parallel, the telogenic phase decreased by:

6.76% at T_2 (9.1% at T_1) in Group 1

10 27.7% at T_2 (9.6% at T_1) in Group 2

4.16% at T_2 in Group 3, for which, however, an increase in the telogenic phase (of about 1.88%) is actually found at T_1 .

D) The haematochemical analyses gave values within the norm for all the Groups 1, 2 and 3.

15 E) Pull test:

The mechanical tensile strength of the hair increased significantly in Groups 1 and 2, whereas it remained virtually unchanged in the placebo Group 3.

20 F) Wash test. This test makes it possible not only to quantify the number of hairs lost after shampooing, but also, by means of a suitable microscopic analysis, to evaluate the phase of the cycle in which the bulb was found when the hair fell out: pathological loss (telogenic) or phase of physiological exchange (exogenic).

25 The test results are given in the graph of Figure 3 in the attached drawings. In this graph, the number of hairs lost during washing for the individuals of the three groups mentioned above is given on the y-axis, and the said times T [T_0 (before starting the treatment); T_1 (at the end of the 60 days of treatment); T_2 (30 days after stopping the administration)] are given on the x-axis, under which are tabulated the values found.

30 As may be seen, the number of hairs lost in the wash test

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decreases significantly for the treatment process in Groups 1 and 2 (solid lines), whereas it remains unchanged in the placebo Group 3 (dashed line in the graph).

In addition, by analysing the bulbs of the lost hairs, the following
5 important observation was made. In Group 3 treated with placebo, more than 90% of the lost hairs were in the telogenic phase (pathological loss) and only 3% were in the exogenic phase (physiological loss).

In Groups 1 and 2 this ratio changes, since the hairs in the exogenic phase are 33% in Group 1 and 46% in Group 2, with a
10 consequent reduction in the hairs in the telogenic phase, which was found to be 63% in Group 1 and 52% in Group 2.

Thus, in Groups 1 and 2, among the lost hairs, there was a significant decrease in the percentage of hairs in the telogenic phase (pathological loss) and a proportionate increase in the percentage of
15 hairs in the exogenic phase (physiological loss by exchange).

G) The side effects were mild and all disappeared as the treatment continued, taking care to take the capsule during the main meal, at T_1 .

According to the present invention, it was thus experimentally
20 found that the oral administration to man of a composition containing spermidine, preferably combined with other components such as methionine, bioflavonoids, vitamins and mineral salts, is capable of slowing down and stopping excessive hair loss in the case of telogenic defluvium, and simultaneously of improving the strength and general
25 health of the hair.

The pull test demonstrated that spermidine, either in unmodified form or combined with other micro-nutrients, increases the mechanical tensile strength of the hair.

The trichogram and the wash test made it possible to demonstrate
30 large variations arising in the hair bulb following treatments with

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spermidine in unmodified form or combined with other active components. Not only is the number of hairs lost after washing substantially reduced, but also, among those lost, the number in the telogenic phase (pathological loss) is substantially decreased when compared with the number in the exogenic phase (loss by physiological exchange). Thus, the treatment with spermidine in unmodified form or with spermidine combined with other micro-nutrients has substantially modified the cycle of the hair altered by the telogenic defluvium pathology, returning it to the normal values of physiological exchange.

For the use of spermidine according to the present invention, it is convenient to formulate it in compositions preferably for oral use, and preferably as a dietetic product. It may also be formulated in compositions for topical use on the scalp.

A number of examples, not intended to be limiting, of compositions according to the invention will now be described.

EXAMPLE 1

DIETETIC COMPOSITION FOR MAKING THE HAIR ROBUST AND REDUCING HAIR LOSS

Sealed rigid plant capsules

Each capsule contains:

Active principles

Methionine	300.00	mg
Vitamin C	90.00	mg
25 Polyphenols from <i>Vitis vinifera</i>	5.00	mg
Vitamin E	15.00	mg
Calcium pantothenate	9.00	mg
Zinc (as amino acid chelate)	7.50	mg
Vitamin B ₆	2.00	mg
30 Copper (as amino acid chelate)	1.25	mg

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	Spermidine	0.50	mg
	Folic acid	0.15	mg
	Biotin	0.05	mg
	Excipients		
5	Hydroxypropylmethylcellulose	110.00	mg
	Talc	21.00	mg
	Magnesium stearate	6.50	mg
	Colloidal silica	2.85	mg
	Natural colorants	2.50	mg

10

EXAMPLE 2

DIETETIC COMPOSITION FOR MAKING THE HAIR ROBUST AND
REDUCING HAIR LOSS

Packets to be dissolved in water

Each packet contains:

15	Active principles		
	Methionine	300.00	mg
	Vitamin C	90.00	mg
	Polyphenols from <i>Vitis vinifera</i>	20.00	mg
	Vitamin E	15.00	mg
20	Calcium pantothenate	9.00	mg
	Zinc (as amino acid chelate)	7.50	mg
	Beta-carotene	4.20	mg
	Vitamin B ₆	2.00	mg
	Copper (as amino acid chelate)	1.25	mg
25	Spermidine	0.50	mg
	Folic acid	0.30	mg
	Biotin	0.15	mg
	Excipients		
	Maltodextrin	2 000.00	mg
30	Sodium citrate	350.00	mg

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	Citric acid monohydrate	200.00	mg
	Flavourings	160.00	mg
	Colloidal silica	65.00	mg
	Aspartame	30.00	mg
5	Acesulfame K	7.00	mg
	Natural colorants	3.50	mg

EXAMPLE 3

COSMETIC ATTACK LOTION (initial treatment) FOR MAKING THE
HAIR ROBUST AND REDUCING HAIR LOSS

10	In ampules		
	Each ampule of 10 ml of solution contains:		
	Active principles		
	Spermidine	2 mg	
	Catechin and quercetin complex	40 mg	
15	Methylsulphonylmethane	400 mg	
	Azeoglycine (potassium azeloyl diglycinate)	300 mg	
	Sunflower oil and rosemary oil	5 mg	
	Menthyl lactate	25 mg	
	Calcium pantothenate	16 mg	
20	Biotin	0.15 mg	
	Excipients		
	Ethyl alcohol	4.0	ml
	Fragrance	5.0	mg
	Natural colorants	0.2	mg
25	Purified water	qs	10 ml

EXAMPLE 4

COSMETIC MAINTENANCE LOTION (continuation of treatment) FOR
MAKING THE HAIR ROBUST AND REDUCING HAIR LOSS

In bottles

30 100 ml of solution contain:

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	Active principles		
	Spermidine	5 mg	
	Catechin and quercetin complex	200 mg	
	Methylsulphonylmethane	2 000 mg	
5	Azeoglycine (potassium azeloyl diglycinate)	3 000 mg	
	Sunflower oil and rosemary oil	50 mg	
	Menthyl lactate	250 mg	
	Calcium pantothenate	80 mg	
	Biotin	1.5 mg	
10	Excipients		
	Ethyl alcohol	35 ml	
	Natural colorants	900 mg	
	Fragrance	50 mg	
	Purified water	qs 100 ml	

15

EXAMPLE 5

COSMETIC BALM FOR MAKING THE HAIR ROBUST AND
REDUCING HAIR LOSS

	In bottles		
	100 ml of balm contain:		
20	Active principles		
	Spermidine	10 mg	
	Catechin and quercetin complex	400 mg	
	Methylsulphonylmethane	4 000 mg	
	Azeoglycine (potassium azeloyl diglycinate)	3 000 mg	
25	Sunflower oil and rosemary oil	50 mg	
	Menthyl lactate	250 mg	
	Calcium pantothenate	80 mg	
	Biotin	1.5 mg	
	Excipients		
30	Cetearyl alcohol	5 000 mg	

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	PEG-15 cocopolyamine		5 000 mg
	Oat protein hydrolysate		3 000 mg
	Glycerol		3 000 mg
	Cetyl alcohol		2 000 mg
5	Quaternium-52		1 000 mg
	Phenoxyethanol		300 mg
	Methyl-ethyl-propyl para-oxybenzoates		200 mg
	Fragrance		500 mg
	Colorants		1 000 mg
10	Purified water	qs	100 ml

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CLAIMS

1. Use of spermidine as an active principle in the preparation of a composition for pharmaceutical or dietetic use in man to combat hair loss.
- 5 2. Use of spermidine according to Claim 1, to combat hair loss in the case of the pathology known as telogenic defluvium.
3. Use of spermidine according to Claim 2, to reduce the telogenic phase in the growth cycle of the hair.
4. Use of spermidine according to Claim 1, to make the hair robust.
- 10 5. Composition for pharmaceutical or dietetic use to be administered to man to combat hair loss, characterized in that it comprises spermidine as active principle.
6. Composition according to Claim 5, characterized in that it comprises methionine, vitamin C, polyphenols, vitamin E, calcium
- 15 pantothenate, zinc (as amino acid chelate), vitamin B₆, copper (as amino acid chelate), folic acid and biotin.
7. Composition according to Claim 6, characterized in that it comprises:

Methionine	300.00	mg
20 Vitamin C	90.00	mg
Polyphenols from <i>Vitis vinifera</i>	5.00	mg
Vitamin E	15.00	mg
Calcium pantothenate	9.00	mg
Zinc (as amino acid chelate)	7.50	mg
25 Vitamin B ₆	2.00	mg
Copper (as amino acid chelate)	1.25	mg
Spermidine	0.50	mg
Folic acid	0.15	mg
Biotin	0.05	mg
- 30 8. Composition according to Claim 5, characterized in that it is

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suitable for oral administration.

9. Composition according to Claim 5, characterized in that it is suitable for topical administration, as a lotion or a balm.

10. Composition according to Claim 5, characterized in that it is a
5 product for dietetic use to make the hair robust and to reduce hair loss.

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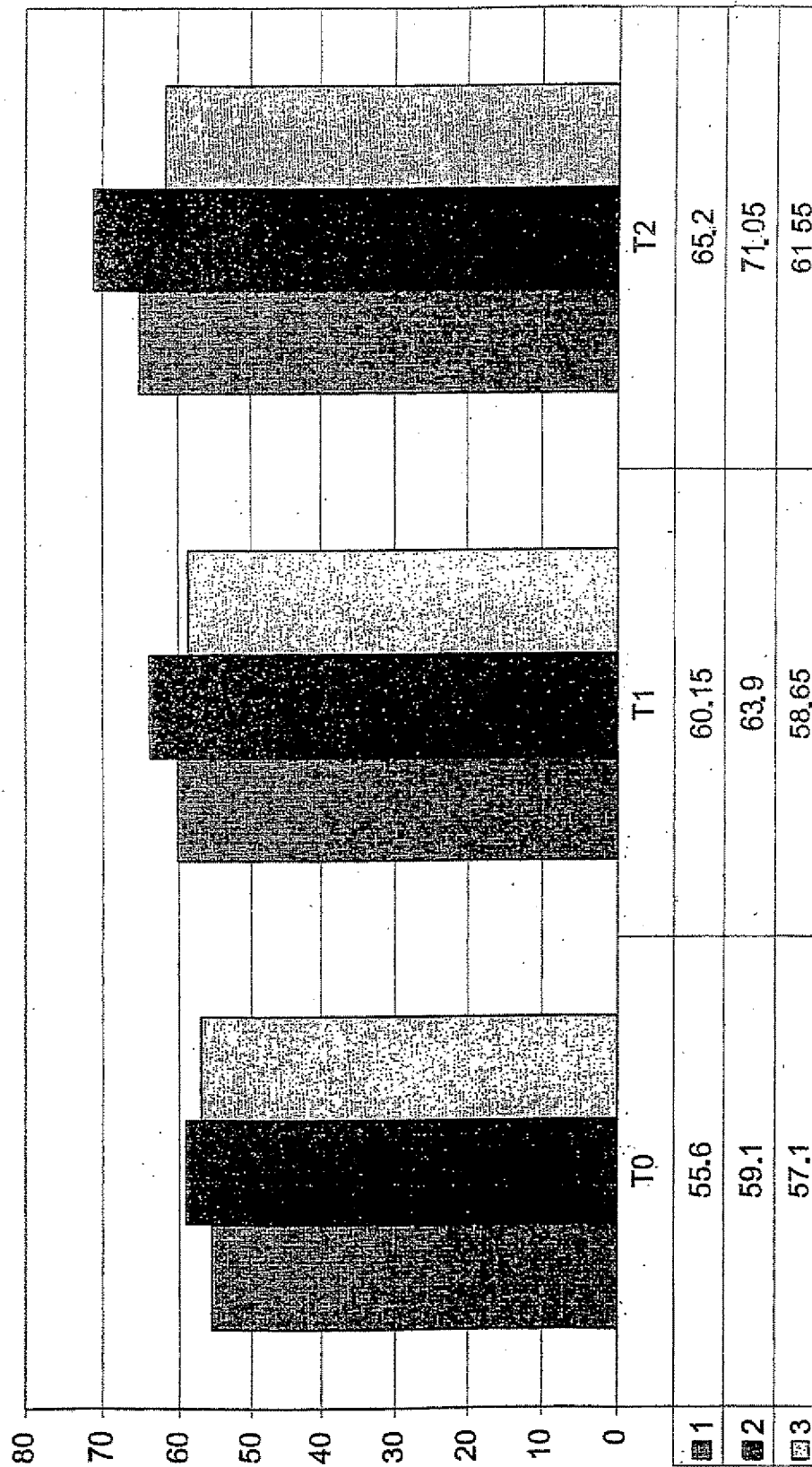


Fig. 1

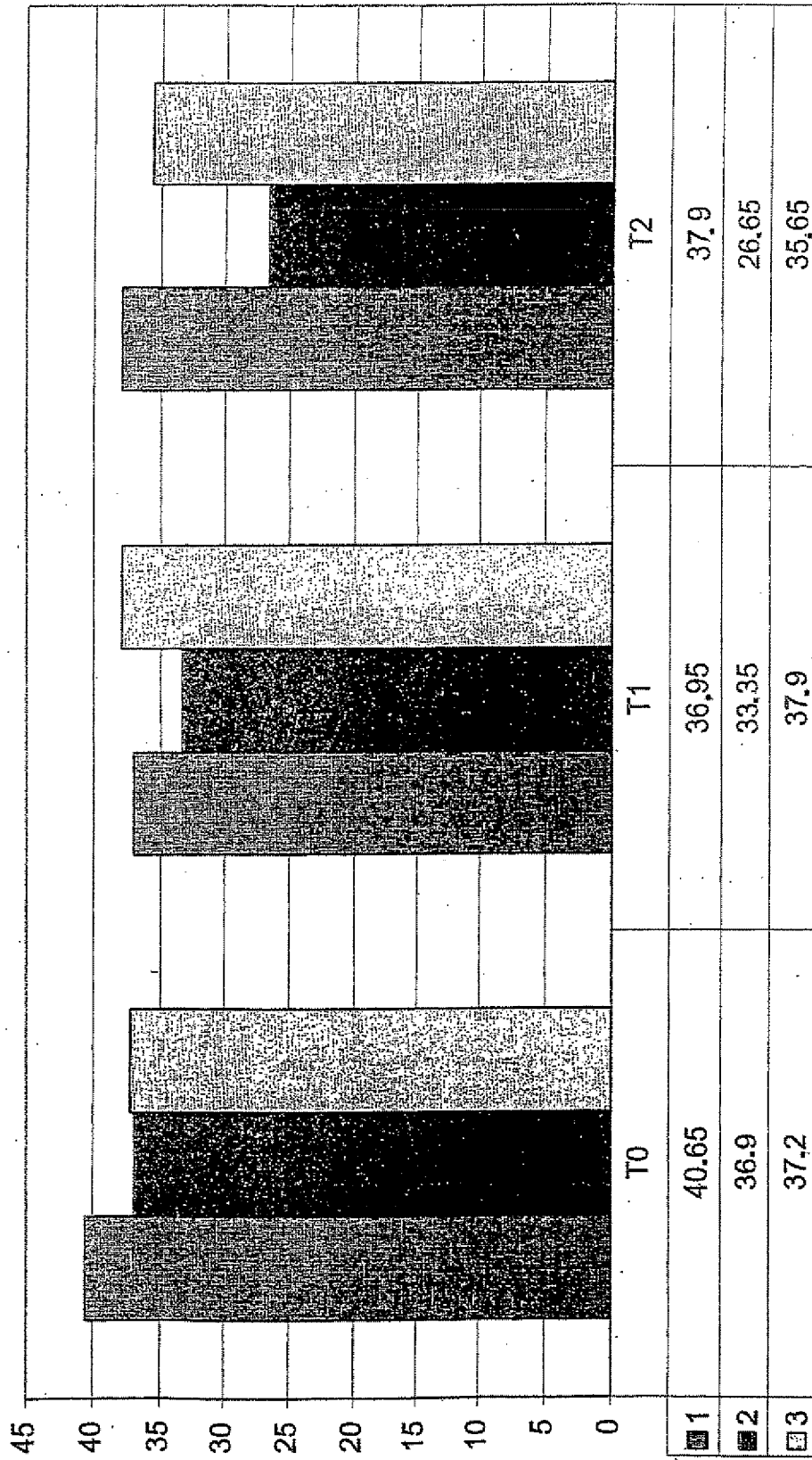


Fig. 2

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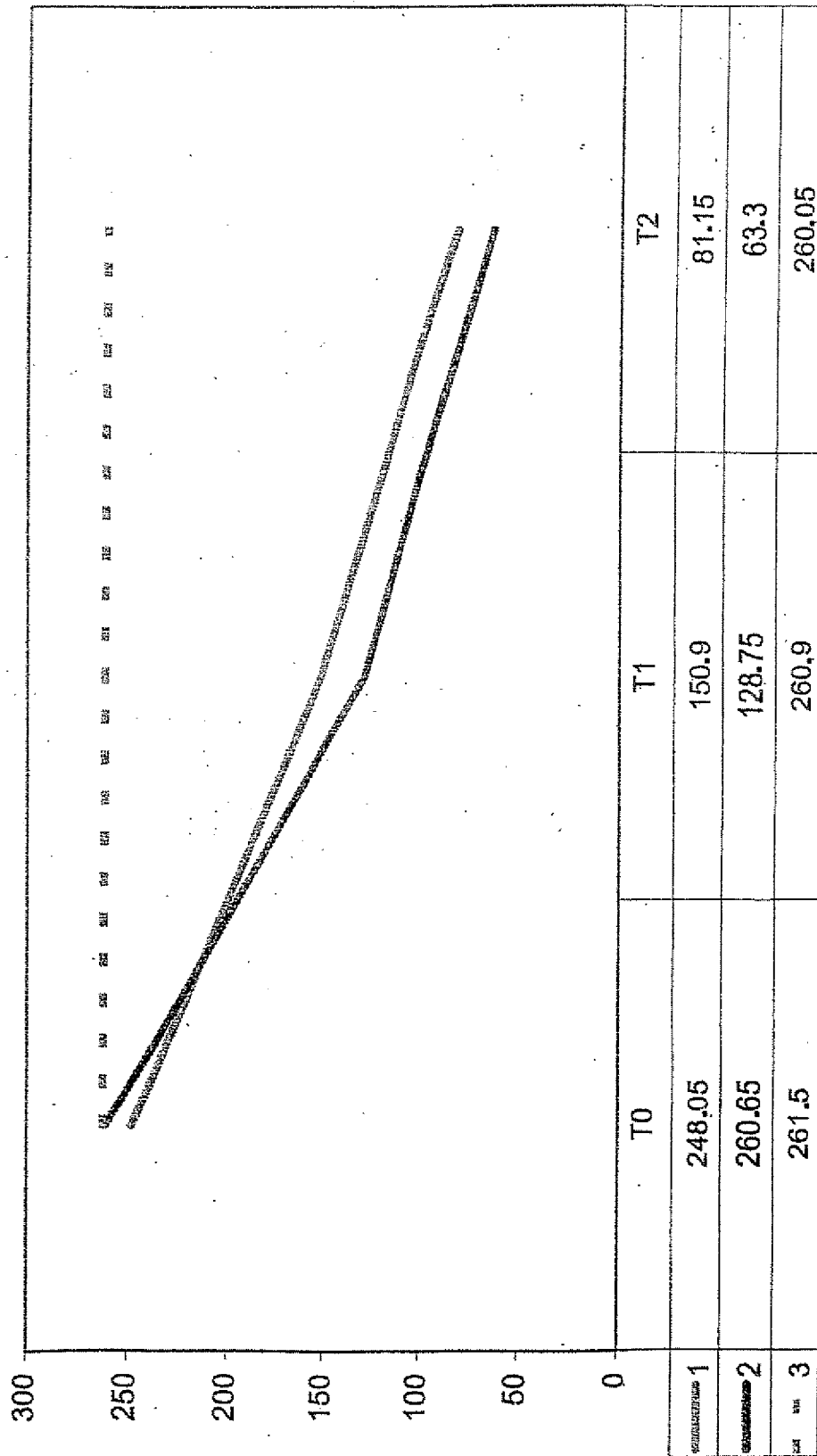


Fig. 3

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/13 A23L1/03 A61K7/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A23L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, BIOSIS, CHEM ABS Data, EMBASE, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	P.I.HYND, M.J.NANCARROW: "Inhibition of polyamine synthesis alters hair follicle function and fiber composition" JOURNAL OF INVESTIGATIVE DERMATOLOGY, vol. 106, no. 2, 1996, pages 249-253, XP008006126 page 249 page 251 page 252, column 2 figures 4,5	1
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☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

18 March 2003

Date of mailing of the international search report

24/03/2003

Name and mailing address of the ISA

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			EP 0806947 A1	19-11-1997
			JP 10513452 T	22-12-1998
			WO 9623490 A1	08-08-1996

CORRECTED VERSION

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
7 August 2003 (07.08.2003)

PCT

(10) International Publication Number
WO 2003/063851 A1

- (51) International Patent Classification⁷: **A61K 31/13**,
A23L 1/03, A61K 7/06
- (21) International Application Number:
PCT/EP2003/000519
- (22) International Filing Date: 17 January 2003 (17.01.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
MI2002A000189 1 February 2002 (01.02.2002) IT
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- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE,
SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI,
SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN,
GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— with international search report
- (48) Date of publication of this corrected version:
19 August 2004
- (15) Information about Correction:
see PCT Gazette No. 34/2004 of 19 August 2004, Section II
- For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: COMPOSITION FOR PHARMACEUTICAL OR DIETETIC USE FOR COMBATING HAIR LOSS

(57) Abstract: The present invention relates to a novel use of the polyamine known as spermidine, i.e. N-(3-aminopropyl)tetram-
ethylenediamine, as an active principle in the preparation of a composition for pharmaceutical or dietetic use in man for combating
hair loss.

WO 2003/063851 A1

